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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Jonathan S. Stamler

Application No.: 08/616,371

Group Art Unit: 1654

Filed: March 15, 1996

Examiner: B. Celsa

For: METHODS FOR PRODUCING AND USING S-NITROSOHEMOGLOBINS



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BRIEF ON APPEAL

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

A four-month extension of time is requested to file a Brief on Appeal pursuant to the Notice of Appeal filed on December 3, 1998 and received in the U.S. Patent and Trademark Office on December 7, 1998. A petition for the extension of time is enclosed together with the fee set forth in 37 C.F.R. §1.17(c).

This is an appeal from the Office Action mailed from the U.S. Patent and Trademark Office on June 5, 1998. A Notice of Appeal was filed on December 3, 1998 and was received in the U.S. Patent and Trademark Office on December 7, 1998. The fee for filing an appeal brief is enclosed. The balance of this appeal is set forth under appropriate headings, as specified by 37 C.F.R. §1.192(c).

I. REAL PARTY IN INTEREST

The real party in interest is Duke University Medical Center, Erwin Road, Durham, North Carolina 27710. Duke University Medical Center is the Assignee of the entire right, title and interest in the subject application, by virtue of an Assignment recorded on May 20, 1996 at reel 7967, frame 0588.

II. RELATED APPEALS AND INTERFERENCES

Patent Application Number 08/667,003, which is a continuation-in-part of the subject application, is also on appeal. A Notice of Appeal for Patent Application Number 08/667,003 was mailed on December 8, 1998, and was received by the United States Patent and Trademark Office on December 11, 1998

III. STATUS OF CLAIMS

Claims 1-3 and 6-8 have been canceled. Claims 4, 5, 9-14, 28 and 29 have been allowed. Claims 15 through 27 have been finally rejected, and a copy of these claims appears in the Appendix of this Brief.

IV. STATUS OF AMENDMENTS

An Amendment After Final Action was mailed to the United States Patent and Trademark Office on August 5, 1998. In an Advisory Action mailed from the United States Patent and Trademark Office on September 8, 1998, the Examiner indicated that the proposed Amendment After Final Action would not be entered.

V. SUMMARY OF INVENTION

The invention relates to methods of treating a mammal for various diseases or medical conditions characterized by abnormalities in nitric oxide and/or oxygen metabolism, comprising administering to the mammal S-nitrosohemoglobin ("SNO-hemoglobin" or "SNO-Hb"; also,

"SNO-Hb(FeII)O₂," referring specifically to S-nitroso-oxyhemoglobin; also, "SNO-Hb[FeII]" referring specifically to S-nitroso-deoxyhemoglobin; also "SNO-metHb," referring specifically to S-nitroso-methemoglobin), or a composition comprising S-nitrosohemoglobin, which may also comprise a thiol or an S-nitrosothiol. See, for example, page 13, line 20, to page 14, line 3. Another therapeutic combination in the method is hemoglobin and a low molecular weight thiol or nitrosothiol. The diseases and/or medical conditions include, more specifically, high blood pressure, heart disease, vascular disease, atherosclerosis, lung disease, inflammation, stroke, angina, acute respiratory distress, sickle cell anemia and organ transplantation. See, for example, page 15, line 7 to page 16, line 11 of the specification. A further method of the invention is a method for enhancing the preservation of an excised organ, comprising storing the organ in a solution comprising SNO-Hb(FeII)O₂.

For Claims 15, 26 and 27, support can be found, for example, on page 13, line 29 to page 14, line 3 and on page 15, line 25 to page 16, line 11. For Claims 16 and 17, support can be found, for example, on page 8, lines 1-9. For Claim 18, support can be found on page 5, lines 28-34 and on page 3, lines 3-7, for instance. Claim 19 is supported by statements on page 27, lines 9-16, page 29, lines 3-13, and on page 14, lines 8-9. Support in the specification for Claim 20 is found at page 3, lines 7-13. For Claim 21, see especially page 13, line 33 to page 14, line 1, and page 3, lines 11-13.

VI. ISSUES

There are four issues for review.

The first issue is whether Claims 15-27 are unpatentable under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. More specifically, Claims 15-27 are said to be indefinite as to the mode of administration and the administered amounts.

The second issue is whether Claim 15 is unpatentable under 35 U.S.C. § 102(b) as anticipated by Stamler *et al.*, WO 93/09806.

The third issue is whether Claim 15 is unpatentable under 35 U.S.C. § 103(a) as obvious over Stamler *et al.*, WO 93/09806. This third issue stems from a rejection raised as an alternative to the rejection that defines the second issue.

The fourth issue is whether Claim 15 is unpatentable, under 35 U.S.C. § 103(a) as obvious in view of Feola *et al.*, US 5,439,882, Klatz *et al.*, 5,395,314 and Hunter, US 5,152,979.

VII. GROUPING OF CLAIMS

The rejected claims do not stand or fall together as one group, but can be divided into four groups as follows.

- (i) Claim 22 is drawn to a method for enhancing the preservation of an excised organ, comprising storing the organ in a solution comprising SNO-Hb(FeII)O₂. The objective of the method of Claim 22 is to preserve the viability of an excised organ, which is an entirely different objective from that of the other claims drawn to methods of treatment of a living mammal or human patient. The method of Claim 22 -- using a solution comprising SNO-Hb(FeII)O₂ to store the organ -- is entirely different from the methods of the other claims, which involve administering SNO-Hb, Hb, or a composition comprising these proteins, to a whole mammal or human.
- (ii) Claims 23-25 are drawn to a method for treating a human with sickle cell anemia, comprising administering to the human a preparation comprising SNO-Hb(FeII)O₂. The method of Claims 23-25 specifically calls for a human with the disease sickle cell anemia and specifically requires the use of SNO-oxyhemoglobin, which can be used for oxygen delivery, optionally in combination with a thiol or an S-nitrosothiol. Thus, the method of Claims 23-25 is different from the methods of the other claims.
- (iii) Claim 15 is drawn to a method for regulating delivery of oxygen and NO to a mammal, comprising administering to the mammal a mixture of a low molecular weight thiol or nitrosothiol and hemoglobin or S-nitrosohemoglobin. The method of Claim 15 includes use of the combination of hemoglobin and low molecular weight thiol or nitrosothiol. The use of this combination is not a part of any other claim. Thus, the manner in which the method is carried

out is fundamentally different from the other methods in which a form of S-nitrosohemoglobin or a composition comprising S-nitrosohemoglobin is administered to a mammal or a human.

(iv) Claims 16-21, 26 and 27 are another group of claims that do not stand or fall with the other claims. Claims 16-21, 26 and 27 are drawn to methods in which a mammal or human is treated for a condition by the administration of SNO-hemoglobin or a composition comprising SNO-hemoglobin. The method of Claims 16-21, 26 and 27 differs from that of the other claims in objective and in the method in which SNO-hemoglobin is used to achieve its result.

VIII. ARGUMENT

(i) Rejection of Claims 15-27 Under 35 U.S.C. § 112, Second Paragraph

The first issue for review is whether Claims 15-27 are unpatentable under 35 U.S.C. § 112, second paragraph. Claims 15-27 were rejected, as they were said to be indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. More specifically, Claims 15-27 were said to be indefinite as to the mode of administration and the administered amounts.

In an Amendment After Final Action mailed to the United States Patent and Trademark Office on August 5, 1998, Claims 15, 16 and 18-23 (Claim 17 is dependent on Claim 16) were amended to include the phrase "an effective amount of," as the Examiner suggested in the Office Action dated June 5, 1998. In the Advisory Action dated September 8, 1998, the Examiner stated, "It is noted that the amendment of claims 15-16 and 18-23, if entered, would overcome the outstanding indefinite rejection of these claims." However, the Amendment After Final Action was not entered.

(ii) Rejection of Claim 15 Under 35 U.S.C. § 102(b)

The second issue for review is whether Claim 15 is unpatentable under 35 U.S.C. § 102(b). Claim 15 was rejected as being anticipated by Stamler *et al.*, WO 93/09806.

WO 93/09806 (Stamler *et al.*) describes the *in vitro* synthesis of various S-nitrosoproteins and nitrosylated amino acids, and demonstrates vasodilatory effects and anti-platelet effects of some of the S-nitrosoproteins.

As stated in the Declaration of Jonathan S. Stamler and the Declaration of Joseph Bonaventura (executed Declarations mailed to the United States Patent and Trademark Office on February 27, 1998 and March 12, 1998), at the time the subject application was filed, it was not known that S-nitrosohemoglobin could be made *in vitro*, or could exist under physiological conditions. Thus, a therapy using a combination of a low molecular weight thiol or nitrosothiol and S-nitrosohemoglobin could not have been known and could not have been obvious.

No therapy using a combination of low molecular weight thiol or nitrosothiol and hemoglobin is taught or suggested in WO 93/09806. Nowhere is the administration of hemoglobin alone or in combination with anything else taught or suggested.

(iii) Rejection of Claim 15 Under 35 U.S.C. § 103(a)

The third issue for review is whether Claim 15 is unpatentable under 35 U.S.C. § 103(a) as obvious over Stamler *et al.*, WO 93/09806.

WO 93/09806 (Stamler *et al.*) describes the *in vitro* synthesis of various S-nitrosoproteins and nitrosylated amino acids, and demonstrates vasodilatory effects and anti-platelet effects of some of the S-nitrosoproteins.

As stated in the Declaration of Jonathan S. Stamler and the Declaration of Joseph Bonaventura (executed Declarations mailed to the United States Patent and Trademark Office on February 27, 1998 and March 12, 1998), at the time the subject application was filed, it was not known that S-nitrosohemoglobin could be made *in vitro*, or could exist under physiological conditions. Thus, a therapy using a combination of a low molecular weight thiol or nitrosothiol and S-nitrosohemoglobin could not have been known and could not have been obvious.

No therapy using a combination of low molecular weight thiol or nitrosothiol and hemoglobin is taught or suggested in WO 93/09806. Nowhere is the administration of hemoglobin alone or in combination with anything else taught or suggested.

On page 21, lines 17-18, WO 93/09806 suggests that the administration of "S-nitrosoproteins would deliver NO, and thus nitrosylate hemoglobin or myoglobin in order to increase oxygen binding." It might be inferred from this that the administration of S-nitrosoproteins alone might convert hemoglobin already present to S-nitrosohemoglobin. However, WO 93/09806 does not show that S-nitrosohemoglobin can even be made, *in vitro* or *in vivo*. There is no suggestion in this that hemoglobin be administered with anything else. As for the suggestion that nitrosylated hemoglobin would increase oxygen binding, no data are presented in WO 93/09806 to support this. On the contrary, the prior art teaches that hemoglobin acts as a scavenger of NO \cdot . See Lancaster, J.R. et al., *Proc. Natl. Acad. Sci., USA* 91:8137-8141 (1994), for example, Figure 3A and 3B, page 8139 (reference cited as AV3). Low molecular weight nitrosothiols can act as donors of NO. The reaction of NO with hemoglobin produces NO $_3^-$ and methemoglobin, which is not capable of binding oxygen. See also Furchgott, R.F., "Bioassays with Isolated Vascular Tissue for Endothelium-derived Relaxing Factor, Nitric Oxide and Nitric Oxide Donors," pages 567-581 In *Methods in Nitric Oxide Research*, Feelisch, M. and J.S. Stamler, eds., John Wiley & Sons, Chichester (1996), especially the section entitled "Hemoglobin (Hb)" on page 578 (reference provided as Exhibit 1 with Amendment After Final Action mailed to the United States Patent and Trademark Office on August 5, 1998).

On page 23, lines 11-15, WO 93/09806 states: "An additional embodiment of the invention involves the *in vivo* nitrosylation of protein thiols, by administration of a nitrosylating agent as a pharmaceutical composition. *In vivo* nitrosylation provides a means for achieving any of the physiological effects discussed above, or for regulation of additional protein functions." From this it might be inferred that one could use a "nitrosylating agent" to produce S-nitrosohemoglobin *in vivo*. However, there was no evidence at the time the subject application was filed that S-nitrosohemoglobin could exist.

On page 2, lines 2-13 of WO 93/09806, the possible physiological role of low molecular weight thiols is discussed. However, their administration in a method of therapy is not discussed or implied, either alone or in combination with anything else.

The prior art teaches against the combination of hemoglobin with low molecular weight nitrosothiol. See, for example, Feelisch, M. *et al.*, *Nature* 368:62-65 (1994), wherein it is described that hemoglobin inhibits the vasorelaxant activity of low molecular weight nitrosothiols in a cascade superfusion bioassay system using three precontracted de-endothelialized strips of rabbit aorta (Table 1; reference provided as Exhibit 2 with Amendment After Final Action mailed to the United States Patent and Trademark Office on August 5, 1998).

(iv) Rejection of Claim 15 Under 35 U.S.C. § 103(a)

The fourth issue for review is whether Claim 15 is unpatentable, under 35 U.S.C. § 103(a) as obvious in view of Feola *et al.*, US 5,439,882, Klatz *et al.*, 5,395,314 and Hunter, US 5,152,979.

The teachings of Stamler *et al.* (WO 93/09806) have been described above. As discussed above, the teachings of WO 93/09806 are limited, according to the statements in the Declaration of Jonathan S. Stamler and the Declaration of Joseph Bonaventura.

Feola *et al.* (US 5,439,882) describe cross-linked mammalian hemoglobin, a method of making the same, and a method of using the same as a blood substitute. Reduced glutathione is used in this reference to stop the cross-linking of hemoglobin when using o-adenosine as a cross-linking agent; glutathione becomes part of the cross-linked hemoglobin compound. See column 13, lines 2-6 and lines 27-30. The reported function of glutathione is as an "oxidant trap" (column 13, lines 7-14). Feola *et al.* do not suggest any role of glutathione in carrying out the biological functions of NO. Feola *et al.* do not teach or suggest any method of therapy by the administration of both hemoglobin and a low molecular weight thiol or nitrosothiol.

Klatz *et al.* (US 5,395,314) describe an apparatus and a method to preserve organs in a cadaver or in a brain-dead patient before the organs can be removed for transplantation. The method employs a solution containing perfluorocarbons, which are to act as a blood substitute and transport oxygen in a manner similar to oxygen transport by hemoglobin. The solution may also contain antioxidants as free radical scavengers. Klatz *et al.* do not teach or suggest any S-

nitrosoprotein, nor do they suggest any use of unmodified hemoglobin with either a low molecular weight thiol or nitrosothiol.

Hunter (US 5,152,979) describes a method for treating vascular obstructions, including those which may be caused by infection, sickle cell crisis, malaria and myocardial infarction. The method is to administer to a patient a surface active copolymer of a certain class of hydrophobes to reduce surface tension and friction in blood vessels, thereby reducing the incidence of thrombosis. Hunter does not teach or suggest the use of any form of hemoglobin, either alone or in combination with either a low molecular weight thiol or nitrosothiol.

In any attempt to combine the teachings of the cited references, Klatz *et al.* and Hunter can be eliminated, because they neither teach nor suggest the administration of hemoglobin or of a low molecular weight thiol or nitrosothiol. Combining the teachings of WO 93/09806 with Feola *et al.*, one might find that WO 93/09806 could suggest the administration of S-nitrosoproteins or low molecular weight thiols alone for vasodilation or anti-platelet therapy. However, no reason is given in WO 93/09806 or the other cited references why one might want to combine these agents with anything else, or with hemoglobin in particular. Feola *et al.* might suggest the use of glutathione as an integral part of a cross-linked preparation of hemoglobin, as an "oxidant trap," but does not teach or suggest any other separate use of glutathione, or of other low molecular weight thiols or nitrosothiols. No combination of the cited references can logically suggest the method of Claim 15. Hemoglobin was not known to act as a carrier of nitric oxide until the subject application.

Respectfully submitted,
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APPENDIX

15. (Amended) A method for regulating delivery of oxygen and NO, in various redox forms, in a mammal, comprising administering to the mammal a mixture of a low molecular weight thiol or nitrosothiol and hemoglobin or S-nitrosohemoglobin.
16. A method for delivering NO in a mammal, comprising administering to the mammal a blood substitute comprising S-nitrosohemoglobin.
17. The method of Claim 16, in which the blood substitute comprises S-nitrosohemoglobin and low molecular weight S-nitrosothiol.
18. A method for scavenging oxygen free radicals and NO \cdot in a mammal, comprising administering to the mammal a blood substitute comprising S-nitrosohemoglobin.
19. A method for reducing blood pressure in a mammal, comprising administering SNO-Hb to the mammal.
20. (Amended) A method for treating a disease in a mammal, comprising administering SNO-Hb to the mammal, wherein the disease is selected from the group consisting of heart disease, vascular disease, atherosclerosis, lung disease and inflammation.

21. (Amended) A method for treating a medical condition in a mammal, comprising administering SNO-Hb to the mammal, wherein the medical condition is selected from the group consisting of stroke, angina and acute respiratory distress.
22. A method for enhancing the preservation of an excised organ, comprising storing the organ in a solution comprising SNO-Hb(FeII)O₂.
23. A method for treating a human with sickle cell anemia comprising administering to the human a preparation comprising SNO-Hb(FeII)O₂.
24. The method of Claim 23 in which the preparation comprises SNO-Hb(FeII)O₂ and a thiol.
25. The method of Claim 23 in which the preparation comprises SNO-Hb(FeII)O₂ and an S-nitrosothiol.
26. A method for treating a patient having a disease or medical condition characterized by abnormalities of nitric oxide and oxygen metabolism, comprising administering to the patient an effective amount of a preparation comprising SNO-Hb.

27. The method of Claim 26 in which the disease or medical condition is selected from the group consisting of: heart disease, lung disease, sickle-cell anemia, stroke and organ transplantation.